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FORMULATION AND EVALUATION OF TASTE-MASKED AZITHROMYCIN READY-MIX ORAL SUSPENSION

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ABSTRACT

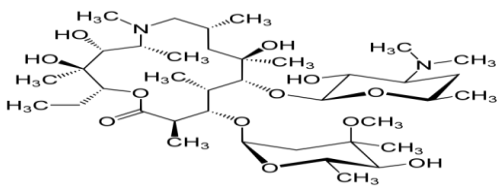
Azithromycin, the macrolide antibiotic, is an azalide derived from erythromycin having bactericidal and bacteriostatic activity by inhibiting the mRNA of the bacteria. It is characterized by its bitter taste which is intensified by the amide group which limits its use for children as the oral liquid form is the most favorable form. The taste can be masked by different techniques and materials of which is the ion-exchange resin, flavors and adsorbing agents. The excipients used to prepare the oral suspension were subjected to compatibility testing and solubility testing then five formulations were designed altering the ion-exchange resin; Kyron T-112 and Magnesium Oxide as a taste adsorbent. Ten healthy volunteers evaluated the taste for each formula. Then the optimized formulation was compared to an imported marketed brand for the taste where the bitterness disappeared, the physical properties are similar to the latter formulations. The maximum drug release percentage is 100.47% in 45 mins which is superior to the market brand and the active ingredient content per volume was 99.31%. It is concluded that, Light Magnesium Oxide efficiently masked the taste of azithromycin in oral liquid suspensions.

KEYWORDS: Ready-mix oral suspension, Taste masking, Azithromycin suspension, Magnesium Oxide taste adsorption.

INTRODUCTION

Azithromycin is a macrolide antibiotic, an azalide derived from erythromycin having bacteriocidal and bacteriostatic activities. It is a white, odourless powder characterized by its bitter taste. Azithromycin is practically insoluble in water but soluble at saliva pH, which readily solubilizes the drug content and exposes it to the taste buds of tongue. Also the amide group intensifies the bitter taste.[1] Azithromycin inhibits the bacterial growth by binding to 50S subunit of the bacterial ribosome, thus inhibiting the transformation of the mRNA.[2][3]

Empirical Formula: $C_{38}H_{76}N_2O_{14}$



Chemical Structure: Figure: 1

Taste Masking

The purpose of taste masking is to improve the pharmaceutical palpability and to attain patient compliance particularly paediatric and geriatric patients. Taste masking techniques involve the use of sweeteners, amino acids, flavors and adsorbents. Cation exchange resins were used to adsorb amine drugs for sustained release action and taste masking. The commonly used cation exchange resins are Kyron and Indion derivatives.

Methods for taste masking:

a- Use of Ion exchange resin and adsorption.
b- Complexation of bitter drug with acceptable pharmaceutical excipients.
c- Use of flavors as fruit flavors and aromatic oils as peppermint
d- Coating the drug particles by lipids using various polymers.
e- Cyclodextrin inclusion and wax embedding.

Taste can be masked by the use of mixture of halogenated oil and surfactants in a fluidized bed by spraying.[4] Quinine taste was masked by complexation with ion-exchange resin, the drug release from the suspension occured within 20 minutes and the suspension was considered stable.[5] Metronidazole taste was masked by Kyron T-114 and Kyron T-134 resin.[6] The bitter taste of azithromycin can be masked by using azithromycin particles as adsorbent for titanium dioxide nanoparticles resulting in a marked improvement of the

taste.[1] The requirement of taste masking is to delay the release of the drug efficiently to eliminate immediate taste.[7] Magnesium Aluminium Silicate (Veegum F) can be used successfully as an adsorbent clay taste masking agent.[8] Azithromycin taste had been masked by the use of Indion-234, Kyron T-112 resins and beta cyclodextrin and light magnesium oxide for fast disintegrating tablets for children among which magnesium oxide was the most effective. Drug release in vitro was found to be 99.9% in 25 minutes. However, for pediatric use the liquid dosage form was preferable.[9]

Other Suspension Excipients

Oral liquid formulations are usually flavored using different fruit juices as grape, citrus fruits, peach, strawberry, peppermint flavors. The use of the buffer was to neutralize the pH to pH 7 – 5.5. The viscosity modifier like gums, xanthan, acacia, guar gum, gelatin and tragacanth were used to maintain the suspendability of the particles and aids in the taste masking by coating the particles preventing them to contact with the taste buds on the tongue.[10]

OBJECTIVES

The objective is to prepare an optimized ready-mix azithromycin suspension with palatable taste to achieve patient compliance.

MATERIALS AND METHODS

Materials

Azithromycin dehydrate (active pharmaceutical ingredient), Sucrose pharma grade, Sucralose, Sorbitol 70% NC solution, Glycerin and Saccharin sodium (Sweetening agent), Sodium methylparaben and Sodium propylparaben (Preservative), Disodium EDTA (Chelating Agent), Dibasic sodium phosphate (Buffer), Xanthan gum (Thickening Agent), Polysorbate 80 (Wetting Agent), Light magnesium oxide (Adsorbent), Kyron T-112BN (Ion Exchange Resin), Sodium chloride Common Ion (For taste balance), Tartazine (Coloring agent), Peppermint flavor (Flavoring agent).

All materials were supplied by Blue Nile Research and Development Centre.

Instruments

Homogenizer (RemiElektrotechnik, India), Electronic Stirrer (RemiElektrotechnik, India), Electronic Sensitive Balance (Axis, Poland), Viscometer (Brookfield, UK), pH Meter (Mi 150, Romania), Dissolution Test Apparatus (Electrolab, India), HPLC (Shimadzu, Japan), Hot Plate (Nuve, Turkey), Infrared Spectrophotomer(Shimadzu, Japan).

Methods

Preformulation Studies

Identification of Azithromycin: The drug was mixed with KBr and pressed into a very thin pellet which was then tested under IR spectrophotometer and the spectrum obtained was interpreted.[11]

Compatibility studies[12][11]

Excipient-drug compatibility was assessed by physical observation and IR spectroscopy of binary mixtures at a 1:1 ratio in the solid state. Samples were stored at 30°C/65% RH and 40°C/75% RH in both open and closed containers for 1 month.

The physical appearance was also observed by mixing each excipient with a weighed amount of API using ratio 1:1 and observations were recorded on days 0, 14 and 30. The samples were mixed with KBr and pressed into a very thin pellet and the spectrum was obtained using the IR. The spectrums obtained are compared with the pure API to ensure compatibility.

Development of the suspension[13]

The following ingredients where used to determine the optimized suspension. Five different formulations where prepared for determination of the optimized suspension.

Table 1: Formulation of Azithromycin Ready-mix suspension.

Material Name	F0	F1	E2	F3	F4
Azithromycin dehydrate (g)	21.05	21.05	21.05	21.05	21.05
Sucrose (g)	250.0	250.0	250.0	250.0	250.0
Sodium methyl paraben (g)	1.125	1.125	1.125	1.125	1.125
Sodium propyl paraben (g)	0.125	0.125	0.125	0.125	0.125
Saccharin sodium (g)	1.0	1.0	1.0	1.0	1.0
Disodium EDTA (g)	1.0	1.0	1.0	1.0	1.0
Sucralose (g)	0.5	0.5	0.5	0.5	0.5
Dibasic sodium phosphate (g)	Qs	Qs	Qs	Qs	Qs
Sorbitol 70 NC solution (g)	50.0	50.0	50.0	50	50.0
Glycerin (g)	50.0	50.0	50.0	50	50.0
Xanthan gum (g)	1.1	1.1	1.1	1.1	1.1
Polysorbate 80 (g)	2.0	2.0	2.0	2.0	2.0
Kyron T-112 BN (g)	-	10.0	20.0	-	-
Light Magnesium Oxide (g)	-	-	-	4.0	6.0
Sodium chloride (g)	2.0	2.0	2.0	2.0	2.0

Peppermint flavor (ml)	0.2	0.2	0.2	0.2	0.2
Tartazine (g)	0.01	0.01	0.01	0.01	0.01
Purified water	To 500 ml	To 500 ml	To 500 ml	To 500 ml	To 500 ml

Procedure

Active drug was weighed accurately and added to 100mL purified water, stirrer for 15 minutes, the weighed Resin/adsorbent was then added to the mixture and stirred for 2 hours. 125ml of purified water heated to 85°C, the weighed quantity of sugar was dissolved in hot water under continuous stirring and heating up to 85°C and the prepared syrup was filtered through 100 mesh and left to cool. Xanthan gum was accurately weighed and added to glycerin under stirring until uniform dispersion was achieved. Sodium methylparaben and Sodium propylparaben were weighed and added to the sugar syrup with continuous stirring. Disodium Edetate, Sucralose and Sodium Chloride where weighed, added to the sugar syrup mixture respectively with continuous stirring. Xanthan Gum- Glycerin mixture was added to the syrup mixture with stirring. Sodium Saccharin was weighed and dissolved into 50ml purified water and added to the syrup mixture. Sorbitol was weighed and added to the sugar syrup. The drug-resin/adsorbent mixture was added to the mixture and let for homogenization for 1 hour. Polysorbate 80 was accurately weighed in a 100ml glass beaker with 20ml purified water. The mixture was heated until completely dissolved. Then it was added to the syrup with continuous stirring. Peppermint flavor was weighed using 10ml pipette and added to the syrup mixture. Tartazine was then weighed and dissolved in 10 ml purified water, then added to syrup. Dibasic Sodium Phosphate 10% solution was prepared for adjustment of pH by weighing 1g and adding to 10ml purified water in a 10ml volumetric flask. The pH of the suspension was checked using a pH meter and adjusted using drops of dibasic sodium phosphate solution. The final volume was made up to 500ml using purified water. For formulation F-0, the active ingredient was directly added to sugar syrup prior to homogenization. The formulation was considered as placebo.

Taste evaluation of optimized formulation

The taste evaluation was performed using taste panel of 10 volunteers in the age group of 19-25 yrs. 5ml of each formulation was held in the mouth for 20 seconds by each volunteer and the bitterness level was recorded using a numerical scale as mentioned below.

Numerical Scale and Equivalent Description

1: Extremely Bitter, 2: Very Bitter, 3: Bitter, 4: Slightly Bitter, 5: Not Bitter

pH[14**]:** pH is a scale used to specify how acidic or basic a water-based solution is. It is defined as the negative logarithm of hydrogen ion concentration.

Viscosity: the viscosity of suspension was determined at ambient condition using Brookfield digital viscometer taking adequate amount of the sample.

Sedimentation Volume: Sedimentation volume F is the ratio of equilibrium volume of sediment (Vu) to the total volume of suspension (Vo).

F = Vu /Vo,

Where, Vu - Volume of sediment and Vo - total volume of suspension.

Sedimentation volume was determined as a function of time. 50ml suspension was transferred to a 100 ml measuring cylinder of 2.5cm diameter. The sedimentation volume F was determined.

Assay[14]

Assay of the optimized suspension was carried out using HPLC. The diluent was prepared by taking 1590 volumes of 0.138% w/v solution of potassium hydrogen orthophosphate, 600 volumes of isopropanol, 480 volumes of methanol and 330 volumes of acetonitrile. The pH of the diluents was adjusted to 8.4 using potassium hydroxide. The sample was prepared by taking the weight equivalent to 0.2g of Azithromycin, and was shaken with 300ml of the diluent in a 500ml volumetric flask until the components dissolved. The volume was made up using the same diluent. The standard was prepared by taking 0.04% w/v (0.04g into 100ml) of Azithromycindihydrate API and dissolved into the diluent. The mobile phase was prepared by taking 40 volumes of a 0.67% w/v solution of dipotassium hydrogen orthophosphate and the pH was adjusted to 8.0, and 60 volumes of acetonitrile. The chromatographic conditions were adjusted and the sample and standard solutions were injected. The specified limit stated in the monograph is from 90% to 110%.

Invitro dissolution studies[14]

The dissolution profile of the optimized formulation was determined using the USP (type II) paddle apparatus with a speed of 45 rpm. The medium used was Sodium dihydrogen phosphate. It was prepared by taking 72.05g of Sodium dihydrogen phosphate and dissolved into 6000 mL of distilled water. The pH was adjusted to 6.0. The sample was prepared by taking 5ml which is equivalent to 200mg Aliquot volume was withdrawn at 10, 15, 30, 45 and 60 min and filtered through 0.45µ membrane filter. The standard was prepared using Azithromycin dihydrate API and dissolving in the medium. The mobile phase was prepared by taking 40 volumes of a 0.67% w/v solution of dipotassium hydrogen orthophosphate and the pH was adjusted to 8.0, and 60 volumes of acetonitrile.

RESULTS AND DISCUSSION

Preformulation Studies, Identification of Azithromycin dehydrate

Infrared spectra of Azithromycin dihydrate was obtained and interpreted by identifying the value of characteristic

peaks. It showed sharp peak at 1650-1850 cm-1 corresponding to stretching vibration of carbonyl group. Figure 2 illustrates the standard IR spectrum of Azithromycin dihydrate from the USP monograph and figure 3 is the spectrum obtained by the sample used in the formulation.

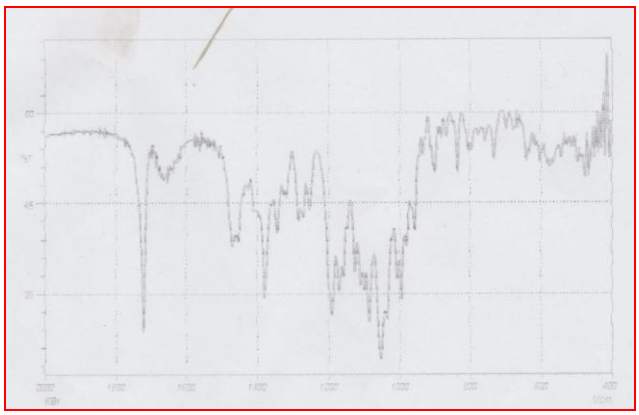


Figure 2: Standard Azithromycin dehydrate.

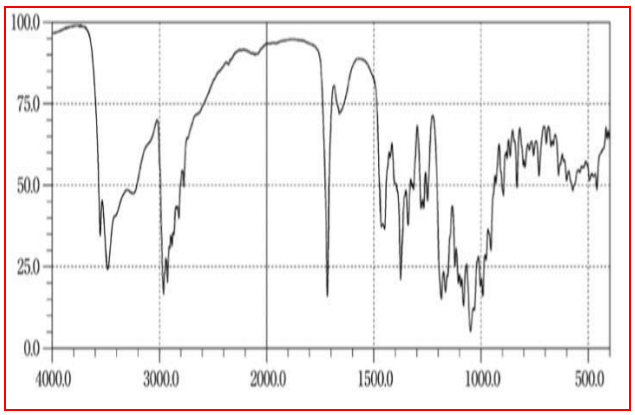


Figure 3: Sample infrared spectruminfrared spectrum Compatibility Studies.

The compatibility based on the appearance of the mixtures on days 0, 14 and 30 shows no interactions observed. There was no change in the appearance of the mixtures on 0, 14 and 30 days. The Active ingredient was found to be compatible with the excipients. Infrared compatibility studies on day 0, 14th and 30th shows that the characteristic peaks of API is observed and no shift on the peak indicating that no physical incompatibility observed between selected excipients and the API as confirmed by IR spectroscopy.

Evaluation of optimized suspension

Taste Evaluation

Ten candidates volunteered to test the formulations for their taste and their remarks were recorded based on the numerical scale. The results are illustrated on table 2 and the general evaluation of the suspensions shown in table 3.

Table 2: Taste evaluation results.

Volunteer	F0	F1	F2	F3	F4
1	1	2	2	3	5
2	1	2	3	3	5
3	1	1	2	2	4
4	1	2	2	3	4
5	2	4	4	5	5
6	1	2	3	3	4
7	2	3	3	5	5
8	1	1	1	2	4
9	1	2	3	4	5
10	1	1	2	3	4
Total score	**12**	**20**	**25**	**33**	**45**

Table 3: General evaluation of the formulations.

No	Test	Observation				
		F0	F1	F2	F3	F4
1	Taste	Extremely bitter	Very bitter	Bitter	Bitter	No bitter
2	pH	8.6	9.01	9.05	9.92	10.06
3	Sedimentation volume F	0.98	0.98	0.96	0.99	0.99
4	Viscosity MBs	456	470	492	512	524

Assay

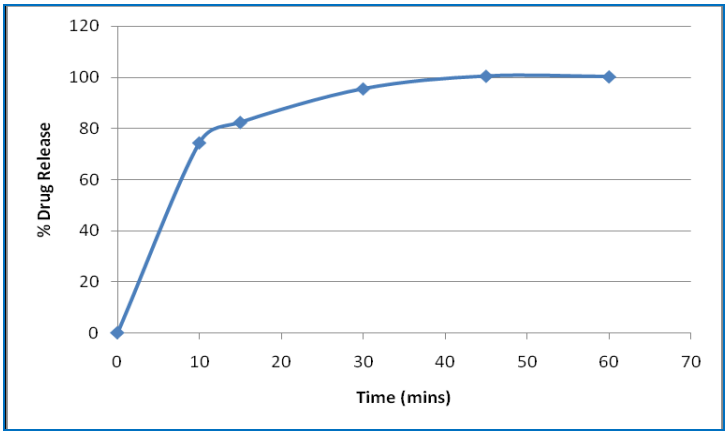
The percentage drug content of the optimized formula F4 was found to be 99.31%, so, it is within the stated limits.

In-vitro Drug Release Profile of F4 Optimized Suspension

The drug release is shown in table 4. The complete release was found to be in 45 mins.

Table 4: Drug Release Profile of F4 Optimized Figure 4 Drug Release Profile of Suspension F4.

Time in min	% cumulative drug release
0	74.37
15	82.38
30	95.52
45	100.47
60	100.25



Comparative Evaluation of the Optimized Formulation F-4 and the marketed sample

Table 6 illustrates the comparative evaluation between F-4 and the marketed sample.

The comparative dissolution results are shown in table 5.

Table 5: Comparative evaluation of the selected optimized suspension and a market's sample.

Sr. No.	Parameter	Observation	
		F4	Market sample
1	Taste	No bitter	No bitter
2	pH	10.06	9.61
3	Viscosity	524	555
4	Sedimentation volume	0.99	0.99
5	Appearance	Yellow viscous liquid	Yellow viscous liquid
6	Assay for Content %	99.31%	99.67%

Table 6: Comparative Dissolution Profile of the Optimized Suspension and a Market's Sample.

Time mins	Cumulative drug Release%	
	F4	Market Sample
0	0	0
10	47.37	72.25
15	82.38	79.68
30	95.5	94.7
45	100.47	100.81
60	100.25	100.65

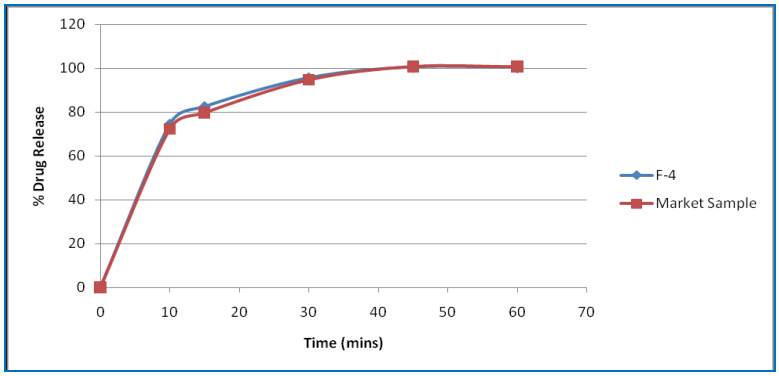


Figure 5: Comparative *In-Vitro* Release profile of F-4 with market sample.

CONCLUSION

Formulation F-4 was found to be satisfactory for masking bitter taste of Azithromycin, out of five different formulations (F-0, F-1, F-2, F-3 and F-4). Optimized formulation; F-4, containing light magnesium oxide at (1:0.3-drug: taste adsorbant ratio) shows better formulation as well as taste masking property over ion exchange resin formulation. The formulation F-4 was compared with a (leading brand) marketed sample and it was found to match the aspects, including taste, pH, viscosity, sedimentation, drug content and drug release.

Recommendations

Real time, Accelerated and in-use stability studies to be carried out. Microbial testing was needed to ensure the success of the preservation. Bioequivalence studies and scale up studies will pass the formulation to human use.

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